MENINGOCOCCAL MULTIVALENT NATIVE OUTER MEMBRANE VESICLE VACCINE, METHODS OF MAKING AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to the U.S. Provisional Application No. 61/057,462 entitled "Meningococcal Multivalent Native Outer Membrane Vesicle Vaccine" filed May 30, 2008. The entire disclosure and contents of the above application is hereby incorporated by reference in its entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] The U.S. Government has rights in this invention.

BACKGROUND OF THE INVENTION

[0003] *Neisseria meningitidis* is a major cause of meningitis and septicemia world-wide. Meningococcal meningitis is an inflammation of the meninges, the membrane lining the brain and the spinal cord. In both meningococcal septicemia and meningococcal meningitis, damage is caused by an uncontrolled localized or systemic host inflammatory response. Group B meningococcal disease currently accounts for at least one half of all meningococcal disease in many countries including North and South America, and Europe. The emergence of a new virulent clone of group B *Neisseria meningitidis*, known as ET5, in Norway in the late 70's has since been responsible for prolonged epidemics in Norway, Cuba, Brazil, and Chile. These epidemics have created serious public health problems and led to intensive efforts to develop an effective group B vaccine in several of the affected countries. The absence of a U.S.-licensed group B vaccine along with the poor performance of the A and C capsular polysaccharide vaccines in children under 18 months have prevented serious consideration of routine childhood vaccination against meningococcal disease.

[0004] *Neisseria meningitidis* is divided into 13 serogroups, of which 9 cause invasive disease (A, B, C(C1, C1-), X, Y, W-135, Z, and L). Five the serotypes are targeted for development of vaccines due to their ability to cause epidemics, including serotypes A, B, C, Y and W135 which are the target of much vaccine research.

[0005] Vaccines against serogroups A, C, Y and W135 of *Neisseria meningitidis* that cause nearly all invasive meningococcal disease are available and are routinely used with excellent results. A suitable vaccine against group B strains of *Neisseria meningitidis* has been more difficult to develop for a variety of reasons. For instance, the capsular polysaccharide which defines the serogroup is ineffective and potentially unsafe for use in a vaccine because it has the same structure as polysialic acid found on certain human cells, specifically blood cells.

[0006] Further adding to the lack of a suitable vaccine is the fact that subcapsular antigens that are surface exposed, such as outer membrane proteins and the lipooligosaccharide (endotoxin), are antigenically variable and/or inconsistently expressed among group B strains. No single antigen has been identified that alone has all the characteristics that are essential for an effective vaccine.

BRIEF SUMMARY OF THE INVENTION

[0007] In one aspect, the present technology provides a vaccine comprising native outer membrane vesicles (NOMVs) obtained from at least two meningococcal strains that have been genetically modified to provide broad based protection. The native outer membrane vesicles include three different sets of antigens based on PorA, LOS, and conserved outer membrane proteins; and the genetically modified strains have been modified to provide enhanced safety based on inactivation of lpxL1, synX, and lgtA genes. The two meningococcal strains can both express LOS having a different LOS core structure and has an alpha chains consisting of glucose and galactose. Each strain may express at least two different PorA subtype proteins or subtype epitopes which are chosen based on the most prevalent of PorA subtypes among group B case isolates. Further, the vaccine may further include a different conserved surface protein with demonstrated capacity to induce bactericidal antibodies is overexpressed in each strain and are taken from the group consisting of FHBP (GNA1870) variants 1, FHBP variants 2, and FHBP variants 3; NadA; App; NspA; TbpA and TbpB.

[0008] In a further aspect, the present technology provides a combination of NOMVs from three genetically modified, antigenically diverse *Neisseria meningitidis* strains. At least one of the stains is selected from (1) H44/76 HOPS-DL which has the following genetic modifications or characteristics: inactivation of the genes synX, lpxL1, and lgtA; insertion of a second porA gene (subtype P1.7-1,1) in the place of opaD; increased expression of NadA; and stabilized high expression of Opc and PorA; (2) 8570 HOPS-G_4L which has the following genetic modifications or characteristics: inactivation of the genes synX, lpxL1, and lgtA; insertion of a second porA gene in place of opaD; increased expression of factor H binding protein variant 1; and stabilized high expression of PorA and Opc; and/or (3) B16B6 HPS-G_2A which has the following genetic modifications or characteristics: inactivation of the genes synX, lpxL 1, and lgtA; insertion of a second porA gene in place of opaD; increased expression of factor H binding protein variant 2; and stabilized high expression of PorA and Opc. The NOMV are prepared without exposure to detergent or denaturing solvents from packed cells or from spent culture medium. The vaccine may be combined with one or more adjuvants and may be administered intramuscularly and/or intranasally.

[0009] In another aspect, the present technology provides a vaccine composition against meningococcal disease, more preferably group B meiningococcal disease, including native outer membrane vesicles (NOMVs) from one or more genetically modified strains of *Neisseria meningitidis*. The one or more genetically modified strains has been modified by: inactivation of the synX gene, inactivation of the lpxL1 gene, inactivation of the lgtA gene in each strain resulting in expression of a shortened or truncated lipooligosaccharides (LOS) that lacks lacto-N-neotetraose tetrasaccharide, and/or insertion of at least one second antigenically different porA gene in place of the opa gene. In another aspect, the genetically modified strain further comprises increased or stable expression of at least one minor conserved outer membrane protein, and/or stabilized expression of at least one outer membrane protein. The at least one second antigenically different porA gene may express at least one PorA subtype protein or subtype epitope selected from the most prevalent of PorA subtypes of meningitidis group β isolates.

[0010] In yet another aspect, the present technology provides a genetically modified vaccine strain of *Neisseria meningitidis* subtype B strain. The genetically modified vaccine